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# Biomedical Advanced Research and Development Authority (BARDA)/Rho STATISTICAL ANALYSIS PLAN

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**BP-I-17-002**

**A Randomized, Double-Blinded, Phase 2 Study to Assess Safety and  
Immunogenicity of Panblok® H7 Vaccine at Three Antigen Dose  
Levels Adjuvanted with AS03® or MF59®**

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**SPONSOR:** Biomedical Advanced Research and Development Authority (BARDA)  
[REDACTED]

**PREPARED BY:** Rho  
[REDACTED]

**AUTHOR(S):** [REDACTED]

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# Biomedical Advanced Research and Development Authority (BARDA)/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

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Approved: \_\_\_\_\_ Date: \_\_\_\_\_  
[Redacted]  
Project Statistician  
Rho

Approved: \_\_\_\_\_ Date: \_\_\_\_\_  
[Redacted]  
Lead Project Statistician  
Division of Clinical Development,  
Biomedical Advanced Research and  
Development Authority (BARDA)

**Document History**

Version	Date	Change(s)	Author
1.0	12 SEP 2017	Initial Draft	
2.0	17 OCT 2018	Deleted synopsis and included relevant information in the text; added study day and duration calculations; added AE displays by subsets; updated visit windows allowable for inclusion in the IPPP; updated type of confidence intervals for analyses; updated interim analysis section to specify only immunogenicity will be analyzed; updated IPPP criteria; deleted imputation method for values <LLOQ or >LLOQ in immunogenicity data due to not being applicable; updated visit window section to not exclude OOW immunogenicity data from the IPPP analyses, changed exploratory scatterplots to heat maps and added an HAI comparison of Guangdong vs. Hong Kong strain; deleted Supplemental Report since all data through Day 394 are being included in the final CSR	

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**LIST OF ABBREVIATIONS**

ADaM	Analysis Data Model
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BARDA	Biomedical Advanced Research and Development Authority
CI	Confidence Interval
CM	Centimeter
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
GMT	Geometric Mean Titer
HAI	Hemagglutination-inhibition
HEENT	Head, eyes, ears, nose and throat
ID	Subject Identifier
IFAP	Immunogenicity Full Analysis Population
IM	Intramuscularly
IP	Investigational Product
IPPP	Immunogenicity Per Protocol Population
KG	Kilogram
M	Meter
MAAE	Medically Attended Adverse Event
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
PIMMC	Potentially Immune-Mediated Medical Condition
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	International System of Units
SMC	Safety Monitoring Committee
SOC	System Organ Class
SPR	Seroprotection Rate

TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization



## **1. INTRODUCTION**

This statistical analysis plan (SAP) was developed after review of protocol BP-I-17-002 and before locking the database or performing any unblinded analyses of the data. The SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the interim analysis and the final Clinical Study Report (CSR). This SAP describes the populations that will be analyzed; the subject characteristics and disposition parameters, the immunogenicity parameters, and the safety parameters that will be evaluated; and details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR. Table, figure, and listing specifications are provided in separate documents.

## 2. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%).” Percentages will be rounded to one decimal place. If n=0, then no percent will be shown. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as “<0.001.”
- All tables, listings, and figures will be presented in Landscape Orientation.
- Courier new 9 font will be used for all displays.
- All analyses will be performed using SAS® System version 9.3 or higher. Figures will be programmed using SAS or R version 3.4.1 or higher.
- Dates will be displayed as ddmmmyyyy (e.g., 24Jan2017).

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

Study days for dates on or after Visit 1 (Day 1) will be calculated as:

$$\text{Study Day} = \text{Date} - \text{Visit 1 Date} + 1$$

For dates prior to Visit 1 (Day 1), study days will be calculated as:

$$\text{Study Day} = \text{Date} - \text{Visit 1 Date}$$

Total duration is calculated as:

$$\text{Duration} = \text{End Date} - \text{Start Date} + 1$$

### **3. STUDY OBJECTIVES**

#### **3.1. Primary Objectives**

##### **3.1.1. Safety**

- To assess the safety and reactogenicity for 8 days postvaccination, inclusive of the vaccination day, (Day 1 through Day 8 and Day 29 through Day 36) of 3 different antigen dosages of Panblok H7 vaccine given with AS03 or MF59 adjuvant (henceforth referred to as investigational products (IP)) administered intramuscularly (IM) on Days 1 and 29, as determined by solicited local and systemic reactogenicity symptoms.

##### **3.1.2. Immunogenicity**

- To assess the serum hemagglutination-inhibition (HAI) antibody seroprotection rate on Day 50 of 3 different antigen dosages of IP administered IM on Days 1 and 29.

#### **3.2. Secondary Objectives**

##### **3.2.1. Safety**

- To assess the occurrence of unsolicited adverse events (AEs), serious adverse events (SAEs) and medically attended adverse events (MAAEs) including a subset of specific potentially immune-mediated medical conditions (PIMMCs) in the 6 treatment groups for 13 months after the first dose of IP.

##### **3.2.2. Immunogenicity**

- To assess the serum HAI antibody titers, seroprotection rates, and seroconversion rates of 3 different antigen dosages of IP through Day 212.
- To assess the serum microneutralization (MN) antibody titers and seroconversion rates of 3 different antigen dosages of IP through Day 212.

## **4. STUDY DESIGN**

This is a randomized, double-blinded, phase 2 study to assess safety and immunogenicity of Panblok H7 vaccine at three antigen dose levels (3.75, 7.5, and 15 µg) adjuvanted with AS03 or MF59. The main purpose of this study is to assess the safety and ability of the recombinant Panblok H7 influenza vaccine adjuvanted with AS03 or MF59, to generate an immune response after 2 doses separated by 28 days in healthy males and nonpregnant females, aged 18 to 49 years, inclusive.

Approximately 360 subjects will be randomized in a 1:1:1:1:1:1 ratio to 1 of the 6 treatment groups.

The study vaccines will be prepared by mixing recombinant Panblok H7 influenza vaccine antigen 1:1 with either MF59 or AS03 adjuvant prior to administration. The study vaccine (0.5 mL) should be administered by IM injection in the deltoid muscle of the arm within 30 minutes of mixing. Each vaccination will be given in a different arm.

The expected study duration is approximately 13.5 months per subject.

Immunogenicity assessments will include serum HAI and MN antibody titers against the following 2 strains: A/Guangdong/17SF003/2016xPR8 (CBER-RG7C, H7N9) (hereafter, referred to as the Guangdong strain) and A/Hong Kong/125/2017xPR8 (RG56B, H7N9) (hereafter, referred to as the Hong Kong strain).

Safety assessments will be based on solicited AEs (local and systemic reactogenicity symptoms) occurring within 8 days of each vaccination, treatment-emergent unsolicited AEs occurring through Day 50, and treatment-emergent SAEs, MAAEs, and PIMMCs throughout the study.

Safety for each subject will be assessed from the time of the first dose of IP through 12 months following the last dose of IP.

## **5. ANALYSIS POPULATIONS**

### **5.1. Safety Population**

The safety population will include all subjects who are randomized and receive at least one IP administration. Each subject will be analyzed as part of the treatment group corresponding to the actual treatment received. The safety population will be used for all safety analyses.

### **5.2. Immunogenicity Full Analysis Population**

The immunogenicity full analysis population (IFAP) will include all subjects who are randomized, received at least one vaccination, and have determinate assay results at any post-vaccination visit. Each subject will be analyzed as part of the treatment group assigned by randomization, regardless of the treatment actually received. The IFAP will be used to analyze serum hemagglutination-inhibition (HAI) antibody titers and seroprotection rates (SPRs) at Visit 7 (Day 50) only.

### 5.3. Immunogenicity Per Protocol Population

The immunogenicity per protocol population (IPPP) will include all subjects who meet the following criteria:

- Are in the IFAP.
- Received a full dose of IP at Visit 1 (Day 1) and a full dose of IP at Visit 4 (Day 29).
- Received the correct treatment as assigned by randomization.
- Had no other major protocol deviations that may have an impact on immunogenicity assessments. These are identified by a review of protocol deviations by BARDA.
- Received a Visit 4 (Day 29) vaccination within  $\pm 7$  days of the expected visit date.
- Had a Visit 7 (Day 50) immunogenicity sample collected within -3 to +10 days of the expected visit date.

All immunogenicity analyses will be performed on the IPPP by the treatment group actually received. If more than 10% of subjects are excluded from the IPPP, all immunogenicity analyses will be performed on the IFAP and IPPP populations at all timepoints.

## 6. VALIDATION AND QUALITY CONTROL PROCEDURES

Validation and quality control of datasets, tables, listings and figures will be performed as specified in the Statistical Validation Plan.

## 7. STUDY SUBJECTS

### 7.1. Treatment Groups

Approximately 360 subjects will be randomized in a 1:1:1:1:1:1 ratio to 1 of the 6 treatment groups as presented in [Table 1](#).

**Table 1: Treatment Groups**

Treatment Group	Hemagglutinin Antigen ( $\mu$ g)	Adjuvant
A	3.75	AS03
B	7.5	AS03
C	15	AS03
D	3.75	MF59
E	7.5	MF59
F	15	MF59

Separate tables will be created for each adjuvant. Each table that is summarized by treatment group will have columns for each treatment group and an overall column that pools all treatment groups per adjuvant.

Treatment groups will be presented in unblinded reports as shown below:

- Treatment Group A: 3.75µg + AS03
- Treatment Group B: 7.5µg + AS03
- Treatment Group C: 15µg + AS03
- Treatment Group D: 3.75µg + MF59
- Treatment Group E: 7.5µg + MF59
- Treatment Group F: 15µg + MF59

For the interim analysis, treatment groups within the same adjuvant will be randomly ordered and assigned a unique distinct integer from 1 to 3. Adjuvants will also be assigned a random integer of 1 or 2. Treatment groups will be reported in the interim analysis as “Treatment 1”, “Treatment 2”, etc. Adjuvant names will also be masked as “Adjuvant 1” and “Adjuvant 2”.

## 7.2. Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed.

The numbers and percentages of subjects will be presented that complete the following milestones:

- Randomized
- Completed Study
- Early termination from study

Percentages for the number of subjects randomized will not be presented. Percentages for other rows will be based on all subjects randomized. Reasons for early termination from the study will be presented.

Visit completion will be presented in a table as counts and percentages, reporting the status of the visit (completed or missed) and the number of subjects with visits out of window per visit. A listing of subject visit completion status will be presented.

The counts and percentages of subjects qualifying for each analysis population will be presented by treatment group. Percentages will be based on all subjects randomized. A listing of each subject and analysis population inclusion will be presented.

For subjects screened but found to be ineligible, specific inclusion and exclusion criteria not met will be listed.

## 7.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed. Summary statistics for baseline and demographic characteristics will be reported in tables by treatment group and pooled adjuvant group for each analysis population. Summaries by site will also be reported. Demographic characteristics will be summarized based on data collected from the Screening visit and include age (years), race, ethnicity and sex.

Age (years) at the time of Visit 1 (Day 1) will be calculated as an integer according to the following formula:

$$Age = \text{Integer portion of } \frac{\text{Visit 1 Date} - \text{Birth Date} + 1}{365.25}$$

Baseline characteristics will be reported from the screening visit and include body weight (kilograms [kg]), height (centimeters [cm]) and body mass index (BMI) (kg/[meters (m)]<sup>2</sup>). If body weight is reported in pounds, the following formula will be used to convert to kg:

$$\text{Body Weight (kg)} = \frac{\text{Body Weight (pounds)}}{2.2}$$

If height is reported in inches, the following formula will be used to convert to cm:

$$\text{Height (cm)} = \text{Height (inches)} \times 2.54$$

BMI will be calculated by the clinical site staff using the following formula, rounded to 1 decimal place:

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height [m]})^2}$$

#### **7.4. Medical History**

Frequencies and percentages of subjects with previous or current medical conditions or surgeries will be summarized by body system reported on the CRF and treatment group. Data listings will be prepared. Potential body systems assessed are skin, HEENT (head, eyes, ears, nose and throat), respiratory, cardiovascular, gastrointestinal, endocrine/metabolic, genitourinary, neurological, blood/lymphatic, musculoskeletal, hepatic, allergies, and psychological/psychiatric.

#### **7.5. Travel History**

Travel history will be listed for all subjects. Residence outside of the United States for 3 months or more (along with countries of residence and time frames) since 2005 and travel outside of the United States (along with countries visited) since 2005 will be listed.

#### **7.6. Immunization History**

Immunization history within 3 months prior to screening will be listed for all subjects, with vaccination type and date of vaccination.

### **8. STUDY OPERATIONS**

#### **8.1. Protocol Deviations**

Protocol deviations captured in the CRF, including site level protocol deviations, will be listed by site with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

#### **8.2. Investigational Product Administration Adherence**

IP administration adherence for dose 1 at Visit 1 (Day 1) and dose 2 at Visit 4 (Day 29) will be summarized by treatment group and listed. Counts and percentages of subjects receiving any amount or a full amount of both dose 1 and dose 2, separately, will be reported in tables; the denominator will be the number of subjects within each group as randomized. For subjects that receive both doses of IP, the counts and percentages of subjects receiving 2 doses of the same IP or 1 dose of each IP will be summarized. For subjects terminating IP administration early, the reasons for terminating IP administration early will also be presented. For subjects who

received the first IP administration but are found ineligible for the second IP administration, specific inclusion and exclusion criteria not met at Visit 4 (Day 29) will be listed.

Details of IP administration will be listed for each IP administration, including date of IP administration, time of IP preparation, time of administration, location of administration and whether a full dose was received.

## **9. IMMUNOGENICITY EVALUATION**

### **9.1. Overview of Analysis Methods**

All immunogenicity summaries will be performed on the IPPP, as described in Section 5.3, and will include separate summaries using the Guangdong strain and the Hong Kong strain.

All statistical inferences of immunogenicity endpoints are considered exploratory in nature, including unadjusted 95% confidence intervals (CIs) and *p*-values as appropriate.

#### **9.1.1. Handling of Dropouts or Missing Data**

There will be no methods of imputation used for missing data for the summaries or analyses of the primary and secondary endpoints.

Sensitivity analyses will address the impact of missing data. This assumes that subjects with missing data follow the same model as other subjects in their respective treatment arm that have complete data. For seroprotection and seroconversion rates, the antibody titer values will be imputed to define seroprotection and seroconversion.

- Intermittent missing data will first be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data.
- Data missing after subjects discontinue treatment early will then be multiply imputed with the SAS MI procedure using a regression statement adjusting for treatment group and other covariates as appropriate. This method is appropriate for monotone missingness.
- There will be 10 samples imputed for analysis.
- Results of the statistical analysis method on the 10 multiply imputed data sets will be summarized by the SAS MIANALYZE procedure.

#### **9.1.2. Multicenter Studies**

Subjects will be enrolled and treated at 4 study centers. Due to the exploratory nature of the protocol, no formal statistical analyses for the primary and secondary endpoints will be adjusted by site. Exploratory analyses described in the SAP may be provided, and any models generated will use site as a covariate.

#### **9.1.3. Assessment Time Windows**

Allowable visit windows for all scheduled visits are provided in the schedule of assessments in Section 19.1. Immunogenicity data from visits that occur out of window will not be excluded from analyses of the IFAP or IPPP populations.

Unscheduled visits may also occur throughout the study. Data from unscheduled visits will be included in listings but will generally not be included in tabular or graphical summaries. The one exception is if the unscheduled visit occurs during the allowable visit window of a missed visit;



any available immunogenicity data from the unscheduled visit will be included in the summary of the missed visit data.

Early termination visits may occur for any subject terminating the study prior to Visit 10 (Day 394). These visits will be summarized together in tabular summaries, and will be included in listings. As with unscheduled visits, immunogenicity data from early termination visits that occur within the allowable visit window of a missed visit will be included in summaries of the missed visit data.

## **9.2. Immunogenicity Variables**

The primary immunogenicity endpoint for this study is seroprotection at Day 50 based on serum hemagglutination-inhibition (HAI) antibody titers.

Analyses of seroprotection based on serum HAI titers at Day 50 will be prepared as defined in Section 9.2.1.1.

All secondary immunogenicity endpoints are listed below and will be analyzed according to Section 9.2.1.1 (seroprotection and seroconversion endpoints) or Section 9.2.1.3 (serum antibody titer endpoints).

- Serum HAI antibody titers at Screening and Days 29, 50, 121, and 212.
- Serum microneutralization (MN) antibody titers at Screening and Days 29, 50, 121, and 212.
- Seroprotection at Screening and Days 29, 121, and 212 based on serum HAI antibody titers.
- Seroconversion at Days 29, 50, 121, and 212 based on serum HAI antibody titers.
- Seroconversion at Days 29, 50, 121, and 212 based on serum MN antibody titers.

### **9.2.1. General Reporting Methods**

#### **9.2.1.1. Seroprotection and Seroconversion Reporting**

Seroprotection is defined as an HAI antibody titer  $\geq 1:40$ . Seroconversion is defined as either a pre-vaccination antibody titer  $< 1:10$  and a post-vaccination antibody titer  $\geq 1:40$ , or a pre-vaccination antibody titer  $\geq 1:10$  and a minimum 4 fold rise in post-vaccination antibody titer. Seroconversion is assessed separately for both HAI antibody titers and MN antibody titers.

Each primary and secondary immunogenicity endpoint involving seroprotection and seroconversion rates will be summarized similarly by treatment group and pooled adjuvant assigned. The following summary statistics will be displayed by visit for each visit with applicable data [i.e. Screening (seroprotection only), Visit 4 (Day 29), Visit 7 (Day 50), Visit 8 (Day 121) and Visit 9 (Day 212)]:

- count of subjects with non-missing data at the visit
- count of subjects meeting criteria for seroprotection or seroconversion
- proportion of subjects meeting criteria for seroprotection or seroconversion

- 95% exact (Clopper-Pearson) CI corresponding to the seroprotection or seroconversion rate

As supportive analyses, the specified success criteria for HAI antibody titers are that the 95% lower bound CI are greater than 70% for SPR and greater than 40% for SCR, respectively. The following null hypotheses will be tested within each treatment group:

1.  $H_0$ : SPR for HAI antibody titers at Day 50 is less than or equal to 70%  
 $H_a$ : SPR for HAI antibody titers at Day 50 is greater than 70%
2.  $H_0$ : SCR for HAI antibody titers at Day 50 is less than or equal to 40%  
 $H_a$ : SCR for HAI antibody titers at Day 50 is greater than 40%

The  $p$ -values will be presented along with proportions and corresponding 95% CIs.

In addition, SPRs and corresponding 95% CIs will be displayed graphically by treatment group on Day 50.

#### **9.2.1.2. Sensitivity Analyses of Seroprotection and Seroconversion Endpoints**

For each endpoint of seroprotection or seroconversion, if more than 10% of data are missing, sensitivity summaries will be performed in the same manner as described in Section 9.2.1.1, but accounting for missing endpoint data, using methodology as described in Section 9.1.1.

#### **9.2.1.3. Serum Titer Reporting**

Each secondary immunogenicity endpoint measuring serum titer levels will be summarized similarly by treatment group and pooled adjuvant assigned. The following summary statistics will be displayed by visit for each visit with applicable data [i.e. Screening, Visit 4 (Day 29), Visit 7 (Day 50), Visit 8 (Day 121) and Visit 9 (Day 212)]:

- count of subjects with non-missing data at the visit
- geometric mean titer (GMT) and corresponding geometric standard deviation
- back-transformed 95% CI based on the  $t$  distribution about the GMT
- minimum and maximum values
- median and 1<sup>st</sup> and 3<sup>rd</sup> quartile values

Treatment group summaries of GMTs by visit will be plotted on the  $\log_2$  scale with corresponding 95% CIs. The reverse cumulative distribution of GMTs for HAI and MN antibodies at Visit 7 (Day 50) will also be plotted.

A data listing of serum antibody titers will be prepared, which will include seroprotection (for HAI antibody titers only) and seroconversion status (for HAI and MN antibody titers separately) at each applicable visit.

#### **9.2.1.4. Sensitivity Analyses of Serum Titer Endpoints**

For each endpoint of serum antibody titers, if more than 10% of data are missing, sensitivity summaries will be performed in the same manner as described in Section 9.2.1.3, but accounting for missing endpoint data, using methodology as described in Section 9.1.1.

#### **9.2.2. Exploratory Immunogenicity Analyses**

Exploratory immunogenicity analyses will be performed on the IPPP by the treatment actually received.

For SPRs and GMTs at Visit 7 (Day 50), the following groups will be compared:

- Within AS03 adjuvant
  - 3.75 µg (Group A) vs. 7.5 µg (Group B)
  - 3.75 µg (Group A) vs. 15 µg (Group C)
  - 7.5 µg (Group B) vs. 15 µg (Group C)
- Within MF59 adjuvant
  - 3.75 µg (Group D) vs. 7.5 µg (Group E)
  - 3.75 µg (Group D) vs. 15 µg (Group F)
  - 7.5 µg (Group E) vs. 15 µg (Group F)

The null hypothesis for each of the comparisons is that there is no difference between the 2 groups. Each alternative hypothesis is that there is a difference between the 2 groups. Significance will be declared at the two-sided  $\alpha=0.05$  level. Due to the exploratory nature of these endpoint analyses, no adjustments will be made for multiple comparisons.

Seroprotection rate will be compared between groups using a two-sided Fisher's exact test. Risk differences will be displayed with corresponding 95% exact unconditional CIs (based on the Santner and Snell method) and  $p$ -values.

Serum HAI and MN antibody titers (log-transformed) will be compared between groups using a  $t$ -test. Geometric mean ratios will be displayed with corresponding 95%  $t$ -type CIs and  $p$ -values.

#### **9.2.3. Serum HAI and MN Antibody Titer Correlations**

Serum HAI and MN antibody titers will be plotted as a heat map with a regression line on the  $\log_2$  scale against each other by visit. The Pearson correlation coefficient will be presented with corresponding  $p$ -value. Similar plots will be created to compare HAI antibody titers between the Hong Kong and Guangdong strains.

These analyses will be performed on the IPPP by the treatment actually received.

### **9.3. Examination of Subgroups**

No subgroups will be analyzed.

### **9.4. By-site Analyses**

No by-site analyses are planned.

## **10. SAFETY EVALUATION**

### **10.1. Overview of Safety Analysis Methods**

All safety analyses will be carried out using the safety population defined in Section 5.1 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

In addition to the reporting of primary and secondary safety endpoints, safety will be also summarized in each dose group through the reporting of vital signs, physical examination findings, and changes in routine laboratory values.

Listings will be prepared for all safety measurements. All listings will be sorted in order of treatment, subject identifier (ID), and time of assessment (e.g., visit, time, and/or event).

Due to the exploratory nature of this study, no inferential analyses are planned as part of the primary or secondary analyses.

#### **10.1.1. Primary Safety Endpoint**

The primary safety endpoint for the study is all solicited local and systemic reactogenicity symptoms occurring within 8 days of each IP administration, inclusive of the vaccination day.

For the primary safety endpoint, a solicited local or systemic reactogenicity symptom is defined as any of the following occurring within 8 days after each IP administration, inclusive of the vaccination day:

- Solicited local reactions at the injection site: erythema/redness, induration/swelling, and pain
- Solicited systemic reactions: fever, myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills

#### **10.1.2. Secondary Safety Endpoints**

All secondary safety endpoints will be analyzed according to Section 10.2.

- All treatment-emergent serious adverse events (SAEs) occurring during study participation. SAEs are defined in Protocol Section 11.2.1.3.
- All treatment-emergent medically attended adverse events (MAAEs) occurring during study participation. MAAEs are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel (medical doctor) for any reason.
- All treatment-emergent potentially immune-mediated medical conditions (PIMMCs) that occur during study participation. PIMMCs are defined in Section 19.3.
- All treatment-emergent unsolicited adverse events (AEs) occurring during study participation. Unsolicited AEs are defined as all AEs that begin prior to or on

Day 50 that are not defined as a solicited local or systemic reactogenicity symptom, SAE, MAAE or PIMMC.

## 10.2. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term (PT), according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 20.0). The severity of AEs will be classified by the investigator on the eCRF. Each AE is entered on the eCRF once at the highest severity.

Only treatment-emergent AEs (TEAEs), those starting or worsening in severity on or after the first IP administration, are collected on the eCRF. AEs with missing start dates will be considered treatment-emergent.

The following conventions will be used for imputing missing start dates.

- For start dates that are missing the day value with non-missing month and year:
  - If the start year is the same as the year of Visit 1 (Day 1), then do the following:
    - If the start month is the same as the month of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
    - If the start month is not the same as the month of Visit 1 (Day 1), then the start date will be imputed as the first day of the non-missing start month.
  - If the start year is not the same as the year of Visit 1 (Day 1), then the start day will be imputed as the first day of the start month.
- For start dates that are missing the day and month values with non-missing year:
  - If the start year is the same as the year of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
  - If the start year is after the year of Visit 1 (Day 1), the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the date of Visit 1 (Day 1).

End dates will not be imputed.

Separate summaries of solicited local and systemic reactogenicity symptoms and unsolicited AEs will be prepared for combined dose 1 and dose 2 (start dates occurring in the periods of Day 1 through 8 and Day 29 through 36), dose 1 only (start dates occurring in the period of Day 1 through 8) and dose 2 only (start dates occurring in the period of Day 29 through 36). Any unsolicited AE that is an abnormal laboratory result and has a start date on the date of the 2nd IP administration will be included in dose 1 summaries due to the laboratory sample being collected pre-IP administration. Otherwise, unsolicited AEs with start dates on or after the date of the 1<sup>st</sup> IP administration on Day 1 and prior to the date of the 2<sup>nd</sup> IP administration on Day 29 will be included in dose 1 summaries. Similarly, unsolicited AEs with start dates on or after the date of the 2<sup>nd</sup> IP administration on Day 29 and prior to or on Day 50 will be included in dose 2 summaries.

For all summaries of AEs, the count of events that fit the specified criteria will be presented. The number of subjects experiencing at least one event will be described using counts and percentages per treatment group. Percentages will be based on the number of subjects in the

safety population within the treatment arm. For summaries of events occurring after dose 2 only, percentages will be based on the number of subjects in the safety population within the treatment arm who received the 2<sup>nd</sup> IP administration.

The following summaries of all TEAEs will be given for combined dose 1 and dose 2, as well as individually for dose 1 and dose 2:

- AEs by SOC and PT
- AEs by AE Type (Solicited, Unsolicited, SAE, PIMMC and MAAE) and PT
- AEs by SOC, PT and severity
- AEs by SOC, PT and relationship to IP
- AEs by SOC, PT and days of onset
- The count of AEs and percentage of subjects experiencing AEs that fit the following categories:
  - AEs
  - SAEs
  - Severe AEs
  - AEs related to IP
  - AEs leading to early termination of IP
  - AEs leading to study withdrawal
  - AEs leading to death
  - Solicited local reactogenicity events
  - Solicited systemic reactogenicity events
  - Severe solicited local reactogenicity events
  - Severe solicited systemic reactogenicity events
  - PIMMCs
  - Severe PIMMCs
  - MAAEs
  - Severe MAAEs
  - Unsolicited AEs
  - Severe unsolicited AEs
  - Unsolicited AEs related to IP

The incidence of TEAEs will be summarized by treatment group and overall within each adjuvant. If a subject experienced more than one episode of an AE, the subject is counted once for that PT. If a subject had more than one AE in a SOC (or AE type, if applicable), the subject is counted only once in that SOC (or AE type). The summary tables will include incidence

estimates for overall SOC (or AE type) as well as for PTs within each SOC (or AE type). Incidence will be presented for SOC (or AE type) by decreasing frequency overall and then alphabetically and by PT within each SOC (or AE type) by decreasing frequency overall and then alphabetically.

If the same TEAE occurs for a subject on multiple occasions, the TEAE will be categorized according to the highest severity rating for that TEAE in that subject (in order, mild, moderate, severe, life-threatening, and fatal). If the severity of the TEAE is not reported, then the severity of the AE will be counted as unknown.

The investigator is to record their opinion on the relationship of each AE to IP (not related, unlikely related, possibly related, probably related and related). If a subject experiences the same AE multiple times, the event with the strongest relationship to IP will be counted. For summaries of IP-related AEs, the categories of possibly related, probably related and related will be considered IP-related. If the relationship is missing, it will be counted as related in summaries.

Day of onset relative to the most recent IP administration will be dichotomized for summaries as  $\leq 8$  days post IP administration and  $\geq 9$  days post IP administration. If a subject experiences the same AE multiple times, the event with the closest start date to IP administration will be counted.

Solicited local reactogenicity symptoms and solicited systemic reactogenicity symptoms will be summarized by severity with 95% exact (Clopper-Pearson) CIs for dose 1 and dose 2, separately, and combined dose 1 and dose 2.

Unsolicited adverse events will be summarized by severity with 95% exact (Clopper-Pearson) CIs for dose 1 and dose 2, separately, and combined dose 1 and dose 2.

SAEs, MAAEs, PIMMCs, AEs leading to death, life-threatening (grade 4) AEs, AEs leading to early termination of IP, and AEs leading to study withdrawal will be summarized separately in tables by SOC and PT.

In addition, all AEs will be listed in chronological order including ID, age, race, sex, and all related event status information (start and stop dates, whether the event was ongoing, study day of onset, severity, seriousness, relationship to IP, action taken with IP, and outcome). Separate flags will be displayed for solicited local reactogenicity symptoms, solicited systemic reactogenicity symptoms, SAEs, PIMMCs, MAAEs, unsolicited AEs, deaths, AEs leading to treatment discontinuation, and AEs leading to study withdrawal. Additionally, a coding list of PTs and the verbatim text associated with them will be produced.

Separate listings for subsets of AEs meeting the following criteria will be created: SAEs, MAAEs, PIMMCs, AEs leading to early termination of IP, and AEs leading to study withdrawal.

### **10.3. Vaccination Site Examination**

Observations from the vaccine site post IP administration will be summarized by visit and treatment group. Vaccine site examinations will be summarized separately for locations of dose 1 and dose 2. Dose 1 site examinations will occur on Visit 1 (Day 1), Visit 3 (Day 8) and Visit 4 (Day 29); dose 2 site examinations will occur on Visit 4 (Day 29) and Visit 6 (Day 36). Counts and percentages of subjects experiencing pain, erythema/redness and induration/swelling at the injection site will be presented. Summaries of the largest diameter of erythema/redness and

induration/swelling will be presented as well, according to the following categories: <2.5 cm, 2.5-5 cm, 5.1-10 cm and >10 cm.

Vaccine site examination information will also be listed for each subject, dose and visit. Information included will be IP administration date, date of examination, time of examination, days since IP administration, whether a photograph was taken of the abnormality, and all information summarized in vaccination site examination tables described above in this section.

#### **10.4. Clinical Laboratory Evaluation**

Clinical laboratory measurements of serum chemistry and hematology will be performed at a central laboratory. All clinical laboratory data will be reported using the International System of Units (SI). If SI units are not available, laboratory-reported units will be used. Descriptive statistics of laboratory values will be presented for each treatment group and overall. Summaries of actual values and change from baseline values by visit will be presented for quantitative laboratory parameters (e.g., WBC, lymphocytes). Baseline is defined as the last lab value prior to IP administration.

If two or more evaluations occur in the same visit window, the evaluation closest to the target visit day will be selected for inclusion in the analysis. If multiple evaluations are equally close to the target visit day, then the latest evaluation will be selected for inclusion in the analysis.

Clinical laboratory results will receive a toxicity grade as AEs according to Section [19.2](#) and will be presented with the AE displays.

Shift tables will be prepared to display cross-tabulations of the number of subjects experiencing each toxicity grade at baseline compared to other visits by treatment group and clinical laboratory test.

All clinical laboratory values will be presented in a listing.



## **10.5. Vital Signs, Physical Findings, and Other Observations Related to Safety**

### **10.5.1. Vital Signs**

Vital signs parameters of blood pressure (systolic and diastolic) (mmHg), pulse rate (beats/minute), respiratory rate (breaths/minute) and oral temperature (°F) will be summarized and listed for all visits with applicable data. Change from baseline will be displayed. Screening results will be considered baseline for summaries of vital signs data.

Toxicity grading of vital signs as AEs according to Section 19.2 will be collected and presented in the AE displays.

Shift tables will be prepared to display cross-tabulations of the number of subjects experiencing each toxicity grade at baseline compared to other visits by treatment group and vital sign parameter.

All vital signs will be listed in by-subject listings including visit and collection date.

### **10.5.2. Physical Examinations**

Physical examination results of 'abnormal', 'normal' or 'not done' will be collected and summarized in tables for the following body systems: skin, HEENT (head, eyes, ears, nose and throat), neck, thyroid, lungs, heart, abdomen, lymph nodes, and musculoskeletal/extremities. Data listings will be provided including visit and collection date.

## **10.6. Pregnancy Assessment**

Urine pregnancy assessments will be done at Screening and prior to IP administration on Visit 1 (Day 1) and Visit 4 (Day 29). Date, time and result of each pregnancy assessment will be listed for all subjects.

In the case of one or more pregnancies occurring during study participation, a data listing will be prepared to display applicable information, including date of report, method of pregnancy confirmation, delivery date (if applicable), pregnancy termination status and week (if applicable), and any problems or congenital abnormalities present.

## **11. OTHER ANALYSES**

### **11.1. Use of Medications**

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (enhanced version 2017.01). Medications reported on the eCRF will be categorized for analysis as prior or concomitant to IP administration by comparing the medication start and stop dates with the first IP administration dates. Prior medications will have a medication start date prior to the first IP administration date. Concomitant medications will have a medication start on or after the first IP administration date or a stop date on or after the first IP administration date. Medications that fit the criteria for both a prior and concomitant medication will be indicated as such in data listings.

The number and percentage of subjects receiving prior or concomitant medications will be presented overall and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class.

Medication usage will be listed, including Anatomical Therapeutic Chemical (ATC) level 4 coding term, verbatim drug name, preferred drug name, start date, end date, dose (with unit), frequency, route, ongoing status and affiliation with an AE.

The following conventions will be used for imputing missing start dates.

- For start dates that are missing the day value with non-missing month and year:
  - If the start year is the same as the year of Visit 1 (Day 1), then do the following:
    - If the start month is the same as the month of Visit 1 (Day 1), the start date will be imputed as the date of Visit 1 (Day 1).
    - If the start month is not the same as the month of Visit 1 (Day 1), the start date will be imputed as the first day of the non-missing start month.
  - If the start year is not the same as the year of Visit 1 (Day 1), then the start day will be imputed as the first day of the non-missing start month.
- For start dates that are missing the day and month values with non-missing year:
  - If the start year is earlier than the year of Visit 1 (Day 1), the start month and day will be imputed as July 1.
  - If the start year is the same as the year of Visit 1 (Day 1), the start date will be set to the date of Visit 1 (Day 1).
  - If the start year is after the year of Visit 1 (Day 1), the start month and start day will be imputed as January 1.
- Completely missing start dates will be imputed as the date of Visit 1 (Day 1).

End dates will not be imputed.

## 11.2. Prior and Concomitant Immunizations

Non-IP immunizations will be collected beginning 3 months prior to Screening and throughout the study. Prior and concomitant immunizations will be listed in separate listings, including immunization type and date. Missing date parts will be imputed using the same logic as concomitant medication start dates.

## 12. SAMPLE SIZE CONSIDERATIONS

No formal power analyses were conducted since the study objectives require no hypothesis testing. The sample size for this study is approximately 360 subjects, randomized 1:1:1:1:1:1 into 6 treatment groups of approximately 60 subjects each.

Though no hypothesis testing will be performed as part of the primary analyses, [Table 2](#) and [Table 3](#) show the probability of observing a safety event and statistical power to detect seroprotection, respectively, under a hypothetical variety of scenarios. Within each table, separate calculations are performed for each pooled group of interest. Probabilities of detecting an event were calculated using the binomial distribution ([Table 2](#)) and power to detect a difference from a true seroprotection rate of 70% was calculated using an exact binomial test ([Table 3](#)), assuming a two-sided alpha level of 0.05.

**Table 2: Probability of Observing at Least One Event of Interest in a Treatment Group or Pooled Grouping under Different True Event Rates**

True Probability of an Event of Interest	Per Treatment Arm (N=60)	Per Antigen Dosage (N=120)	Per Adjuvant (N=180)	Overall (N=360)
0.005	0.260	0.452	0.594	0.835
0.01	0.453	0.701	0.836	0.973
0.02	0.702	0.911	0.974	0.999
0.05	0.954	0.998	>0.999	>0.999
0.1	0.998	>0.999	>0.999	>0.999

**Table 3: Power for Detecting Observed HAI Seroprotection Proportions Given a True Seroprotection Proportion of 70%**

True Seroprotection Proportion (%)	Observed Seroprotection Proportion (%)	Per Treatment Arm (N=60) (%)	Per Antigen Dosage (N=120) (%)	Per Adjuvant (N=180) (%)	Overall (N=360) (%)
70	80	32.3	64.1	84.7	99.1
	85	71.6	96.8	99.8	>99.9
	90	96.6	>99.9	>99.9	>99.9

### 13. STATISTICAL PROGRAMMING PROCESS

For a detailed explanation of programming and validation processes, please see the Statistical Validation Plan.

#### 13.1. Maintaining the Blind

For all analyses requiring unblinded data from study start through the Day 394 analysis for the final CSR, a blinded programming team consisting of programmers and statisticians will perform all programming tasks (including Study Data Tabulation Model [SDTM] datasets, Analysis Data Model [ADaM] datasets, tables, listings and figures) and all associated validation tasks using dummy treatment groups, which will be randomly assigned. After validation of datasets and displays using dummy treatment groups, an unblinded team of a statistician and a programmer will generate, interpret and report each analysis using appropriate treatment groups and will not modify any programs used to perform analyses.

Any necessary modification of programs due to incorrect coding will be communicated from the unblinded team to the blinded team so that the blinded team can modify the coding while being blinded to treatment groups, after which the unblinded team will then rerun analyses using unblinded data. This process is continued until the unblinded team ensures all data issues have been resolved.

### **13.1.1. Immunogenicity Data**

Immunogenicity data of serum HAI and MN antibody titers may potentially be unblinding as to antigen dose level, as a higher titer level may correspond to a higher antigen dose level. To ensure that no blinded individual may be unblinded by viewing the immunogenicity data, the unblinded statistician will randomly reassign the IDs in the file so that titer levels will be assigned to different subjects than they actually correspond to. Blinded programming tasks will be done only on the reassigned file. The file with correct ID assignments will be used for all unblinded analyses and will only be viewable by unblinded individuals.

## **14. AD HOC SAFETY MONITORING COMMITTEE MEETING**

There are no formal or planned Safety Monitoring Committee (SMC) reviews of safety data. In the event of a study stopping rule being met or other immediate safety concerns, an ad hoc SMC review will be scheduled. The blind will be maintained for all blinded individuals according to Section 13.1. The unblinded statistician will be responsible for presenting data to the SMC. Safety analyses for SMC review will be completed using the safety population.

The study will be stopped for an ad hoc SMC review if any of the below occur:

1. Five or more subjects have generalized urticaria.
2. One or more subjects have injection site ulceration, abscess, or necrosis.
3. One or more subjects have Grade 3 or worse laryngospasm, bronchospasm, or anaphylactic shock within 24 hours of vaccine administration.
4. One or more subjects are withdrawn from further vaccination due to meeting vaccination termination criteria #1-4 in Protocol Section 6.4.1.
5. One or more subjects are withdrawn from further vaccination or from the study by the investigator due to a Grade 3 or higher AE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
6. One or more subjects experience an SAE or PIMMC assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
7. Any Grade 3 or higher abnormality in the same pre-specified laboratory parameter (Protocol Section 11.1.5) occurring in  $\geq 2$  subjects within an individual treatment group or  $\geq 4$  subjects across treatment groups assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
8. Five or more subjects across treatment groups experience a Grade 3 or higher AE or MAAE of the same type (as categorized by Medical Dictionary for Regulatory Activities [MedDRA] preferred term) assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
9. A pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively represent a safety concern in the opinion of the investigator, medical monitor, or BARDA.

For more information about ad hoc SMC meetings and required displays, please see the SMC Charter.

## **15. INTERIM ANALYSES**

An interim analysis will be performed based on cumulative immunogenicity data through Visit 7 (Day 50) for all subjects. Analyses of HAI and MN antibodies against the Hong Kong and

Guangdong strains will be performed separately as data are received. At the interim analysis, the study database (all data through Visit 7 [Day 50]) will be monitored and cleaned per the Data Management Plan.

Data for the interim analysis will be grouped according to treatment group but reported by masked group names. Summaries of pooled treatment groups based on adjuvant will also be included and masked in the interim analysis. Blinding will be maintained for the interim analysis as specified in Section 13.1.

All primary and secondary immunogenicity endpoint analyses will be performed for the interim analysis as specified in Section 9.2. In order to prevent unblinding of any individual subjects, tabular summaries of data will exclude extreme values (minimum and maximum). Figures with individual data points and all listings will not be included in the interim analysis package. The unblinded statistician will be responsible for reporting interim results to BARDA.

Since all active subjects will have completed Visit 7 (Day 50) and no formal statistical comparisons are being made, there will be no penalty for an early look at the data. In addition, no decisions regarding the status of the study will be made as a result of the interim analysis.

## **16. FINAL CLINICAL STUDY REPORT**

The final CSR will be prepared after database lock of all data through Visit 10 (Day 394). All tables, listings and figures mentioned in this report will be included in the final CSR.

Since immunogenicity data are collected through Visit 9 (Day 212), tables and figures containing immunogenicity data will be delivered using real treatment assignments after the lock of all data through Visit 9 (Day 212). However, no by-subject listings will be delivered and blinding will be maintained at a subject level until the database is unblinded after Visit 10 (Day 394).

## **17. CHANGES TO COMPLETED REPORTS**

The study database will be monitored and cleaned per the Data Management Plan for all data through Visit 7 (Day 50) for the interim analysis, Visit 9 (Day 212) for the final immunogenicity analysis and Visit 10 (Day 394) for the final CSR.

## **18. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL**

A supplemental report to the CSR (as specified in Protocol Section 12.1.4.6), that included AE, concomitant medication and concomitant immunization data collected between Visit 9 (Day 212) and Visit 10 (Day 394), is no longer being created, and all applicable information through Visit 10 (Day 394) will be included in one final CSR. This change is a result of delays in receiving immunogenicity data through Visit 9 (Day 212), which made creating multiple reports unnecessary due to a short amount of time between receiving the immunogenicity data and final database lock.

The interim analysis no longer includes safety data, as specified in Protocol Section 12.1.4.4. Due to seeing no major safety concerns in the blinded data, it was determined that the immunogenicity data alone would be necessary prior to final database lock.

Protocol Section 12.1.4.4 specifies that the interim analysis will be presented unblinded at the group level. However, in order to avoid unnecessarily fully unblinding at the group level, interim immunogenicity results were presented using masked treatment assignments prior to database lock through Day 212.

## 19. APPENDICES

### 19.1. Schedule of Assessments

**Table 4: Schedule of Assessments**

Study Visit	Screen-ing	V1	V2 <sup>a</sup>	V3	V4	V5 <sup>a</sup>	V6	V7	V8	V9	V10 <sup>a</sup> (EoS Visit)	ET	Unsch-eduled
Study Day and Visit Window	D-14 to D-3	D1	D4 (±1 D)	D8 (±1 D)	D29 (±3 D)	D32 (±1 D)	D36 (±1 D)	D50 (±3 D)	D121 (±7 D)	D212 (±7 D)	D394 (±7 D)	N/A	N/A
<b>Procedure</b>													
Obtain informed consent	X <sup>b</sup>												
Vital sign measurements <sup>c</sup>	X	X		X	X		X	X				X	X <sup>d</sup>
Height and weight	X												
Medical history	X												
Demographics	X												
Perform subject interview <sup>f</sup>			X	X	X <sup>e</sup>	X	X	X	X	X	X	X	X
Review diary card <sup>g</sup>			X	X	X <sup>e</sup>	X	X	X				X <sup>h</sup>	X <sup>h</sup>
Distribute diary card <sup>g</sup> , thermometer, & measuring tool for injection site reactions and review instructions		X		X	X		X						X <sup>h</sup>
Collect diary card				X	X <sup>e</sup>		X	X				X <sup>h</sup>	X <sup>h</sup>
Record concomitant medications	X <sup>i</sup>	X <sup>e</sup>	X	X <sup>j</sup>	X <sup>e,j</sup>	X	X <sup>j</sup>	X <sup>j</sup>	X	X	X	X	X
Physical examination	X <sup>k</sup>				X <sup>e</sup>			X					
Targeted physical examination <sup>l</sup>		X <sup>e</sup>		X			X					X	X
Urine pregnancy test	X <sup>m</sup>	X <sup>e,m</sup>			X <sup>e,m</sup>								
Review inclusion and exclusion criteria	X	X <sup>e</sup>			X <sup>e</sup>								
Venous blood sample collection for clinical safety laboratory tests <sup>n</sup> (approximately 12 mL)	X			X	X <sup>e</sup>		X					X <sup>d</sup>	X <sup>d</sup>

Study Visit	Screen-ing	V1	V2 <sup>a</sup>	V3	V4	V5 <sup>a</sup>	V6	V7	V8	V9	V10 <sup>a</sup> (EoS Visit)	ET	Unsch-eduled
Study Day and Visit Window	D-14 to D-3	D1	D4 (±1 D)	D8 (±1 D)	D29 (±3 D)	D32 (±1 D)	D36 (±1 D)	D50 (±3 D)	D121 (±7 D)	D212 (±7 D)	D394 (±7 D)	N/A	N/A
Venous blood sample collection for immunogenicity assays (approximately 40 mL)	X				X <sup>e</sup>			X	X	X			
Randomization		X <sup>e</sup>											
Vaccination (per Rho-provided kit assignment)		X			X								
Monitor subject for 30 minutes following vaccination <sup>o,p</sup>		X			X								
Examine vaccination site		X <sup>p</sup>		X <sup>q</sup>	X <sup>e, p, q</sup>		X <sup>q</sup>					X <sup>q, r</sup>	X <sup>q, r</sup>
AE/SAE/MAAE/PIMMC assessment		X	X	X	X	X	X	X	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>	X <sup>t</sup>	X

AE = adverse event; D = day; eCRF = electronic case report form; EoS = end-of-study; ET = early termination; MAAE = medically attended adverse event; N/A = not applicable; PIMMC = potentially immune-mediated medical condition; SAE = serious adverse event; V = visit

<sup>a</sup> Telephone call assessment

<sup>b</sup> Prior to the completion of any study-related procedures

<sup>c</sup> Vital sign measurements include oral temperature, pulse rate, respiratory rate, and blood pressure. Vital signs will be measured before blood is collected. Blood pressure will be measured after subject is seated for at least 5 minutes. Vital signs will be taken both prevaccination and 30 ±5 minutes postvaccination on a vaccination day.

<sup>d</sup> If clinically indicated. The investigator in consultation with the medical monitor will determine whether safety laboratory assessments should be completed.

<sup>e</sup> Prior to vaccination

<sup>f</sup> Ask subject a standard nonleading question to elicit any medically related changes in their well-being. Ask whether they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over the counter medications).

<sup>g</sup> Diary Cards I and III will be used to collect unsolicited and solicited local and systemic reactions 8 days after each vaccination, inclusive of vaccination day (from Day 1 through Day 8 and Day 29 through Day 36); Diary Card II will be used to collect unsolicited AEs from Day 8 through Day 29; Diary Card IV will be used to collect unsolicited AEs from Day 36 through Day 50. Thermometers and measuring tools will be provided to subjects at Visit 1 and replenished as needed.

<sup>h</sup> If applicable, according to the protocol period, collect and review diary card with subject.

<sup>i</sup> Use of all concomitant medications that the subject is taking at the time of the Screening Visit and vaccines received 3 months prior to the Screening Visit will be recorded in the subject's eCRF.

<sup>j</sup> Obtained by interview and by review of diary card completed by the subject.

<sup>k</sup> Any physical examination findings will be collected in the eCRF for medical history data presentation.

- <sup>l</sup> Targeted physical examination will be performed if clinically indicated based on review of interim health status and/or clinical laboratory assessments. Any findings from this examination will be collected in the eCRF for AEs.
- <sup>m</sup> Onsite urine pregnancy test must be performed at the Screening Visit and within 24 hours prior to each vaccination, and pregnancy test results must be final and negative prior to vaccination.
- <sup>n</sup> Clinical safety laboratory tests include a complete blood count with differential, coagulation (partial thromboplastin time and prothrombin time (international normalized ratio) and chemistry including alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, glucose (random, serum), potassium, sodium, total bilirubin, and total protein.
- <sup>o</sup> At Visits 1 and 4, subjects will be monitored for solicited and unsolicited AEs, SAEs, and MAAEs for at least 30 minutes after vaccination. Any concomitant medications taken for these events will be recorded.
- <sup>p</sup> At Visits 1 and 4, complete a 30 ±5 minute postvaccination injection site examination for erythema/redness and induration/swelling and monitor for pain. If a visible injection site abnormality is observed, document with a photograph, if subject consented.
- <sup>q</sup> Examine vaccination site for erythema/redness and induration/swelling and monitor for pain. If a visible injection site abnormality is observed, document with a photograph, if subject consented.
- <sup>r</sup> If the ET or unscheduled visit occurs within 7 days after either of the 2 study vaccinations.
- <sup>s</sup> Only SAEs, MAAEs, and PIMMCs will be collected after Day 50 until the EoS Visit (13 months following the first vaccination).
- <sup>t</sup> If subject declines to participate in an onsite ET visit, study staff should attempt to collect AE/SAE/MAAE/PIMMC and pregnancy information by phone.



## 19.2. Tables for Clinical and Laboratory Abnormalities

The tables for clinical and laboratory abnormalities are presented in [Table 5](#) and [Table 6](#), respectively, according to the FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (September 2007).

**Table 5: Tables for Clinical Abnormalities**

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness <sup>a</sup>	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling <sup>b</sup>	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

<sup>a</sup> In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

<sup>b</sup> Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs <sup>a</sup>	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) <sup>b</sup> (°F) <sup>b</sup>	38.0-38.4 100.4-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	>40 >104
Tachycardia – beats per minute	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minute <sup>c</sup>	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock

<b>Vital Signs<sup>a</sup></b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)</b>
Respiratory rate – breaths per minute	17-20	21-25	>25	Intubation

ER = emergency room

<sup>a</sup> Subject should be at rest for all vital sign measurements.

<sup>b</sup> Oral temperature; no recent hot or cold beverages or smoking.

<sup>c</sup> When resting heart rate is between 60 to 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

<b>Systemic (General)</b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)</b>
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

ER = emergency room; IV = intravenous

**Table 6: Tables for Laboratory Abnormalities**

<b>Serum<sup>a</sup></b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)<sup>b</sup></b>
Sodium – hyponatremia mEq/L	132-134	130-131	125-129	<125
Sodium – hypernatremia mEq/L	144-145	146-147	148-150	>150
Potassium – hyperkalemia mEq/L	5.1-5.2	5.3-5.4	5.5-5.6	>5.6

<b>Serum<sup>a</sup></b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)<sup>b</sup></b>
Potassium – hypokalemia mEq/L	3.5-3.6	3.3-3.4	3.1-3.2	<3.1
Glucose – hypoglycemia mg/dL	65-69	55-64	45-54	<45
Glucose – hyperglycemia Fasting - mg/dL Random - mg/dL	100-110 110-125	111-125 126-200	>125 >200	Insulin requirements or hyperosmolar coma
Blood urea nitrogen mg/dL	23-26	27-31	>31	Requires dialysis
Creatinine mg/dL	1.5-1.7	1.8-2.0	2.1-2.5	>2.5 or requires dialysis
Calcium-hypocalcemia mg/dL	8.0-8.4	7.5-7.9	7.0-7.4	<7.0
Calcium-hypercalcemia mg/dL	10.5-11.0	11.1-11.5	11.6-12.0	>12.0
Magnesium-hypomagnesemia mg/dL	1.3-1.5	1.1-1.2	0.9-1.0	<0.9
Phosphorus – hypophosphatemia mg/dL	2.3-2.5	2.0-2.2	1.6-1.9	<1.6
CPK - mg/dL	1.25-1.5 × ULN	1.6-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Albumin – hypoalbuminemia g/dL	2.8-3.1	2.5-2.7	<2.5	–
Total protein – hypoproteinemia g/dL	5.5-6.0	5.0-5.4	<5.0	–
Alkaline phosphate – increase by factor	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Liver function tests – ALT, AST increase by factor	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10 × ULN	>10 × ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1-1.25 × ULN	1.26-1.5 × ULN	1.51-1.75 × ULN	>1.75 × ULN
Bilirubin – when liver function test is normal; increase by factor	1.1-1.5 × ULN	1.6-2.0 × ULN	2.0-3.0 × ULN	>3.0 × ULN
Cholesterol mg/dL	201-210	211-225	>226	-
Pancreatic enzymes – amylase, lipase	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-5.0 × ULN	>5.0 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; ULN = upper limit of normal.

<sup>a</sup> The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

<sup>b</sup> The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium

value that falls within a grade 3 parameter (125-129 mEq/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

<b>Hematology<sup>a</sup></b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)</b>
Hemoglobin (female) – g/dL	11.0-12.0	9.5-10.9	8.0-9.4	<8.0
Hemoglobin (female) change from baseline value – g/dL	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
Hemoglobin (male) – g/dL	12.5-13.5	10.5-12.4	8.5-10.4	<8.5
Hemoglobin (male) change from baseline value – g/dL	Any decrease – 1.5	1.6-2.0	2.1-5.0	>5.0
WBC increase – cell/mm <sup>3</sup>	10,800-15,000	15,001-20,000	20,001-25,000	>25,000
WBC decrease – cell/mm <sup>3</sup>	2,500-3,500	1,500-2,499	1,000-1,499	<1,000
Lymphocytes decrease – cell/mm <sup>3</sup>	750-1 000	500-749	250-499	<250
Neutrophils decrease – cell/mm <sup>3</sup>	1,500-2,000	1,000-1,499	500-999	<500
Eosinophils – cell/mm <sup>3</sup>	650-1 500	1501-5 000	>5 000	Hypereosinophilic
Platelets decrease – cell/mm <sup>3</sup>	125,000-140,000	100,000-124,000	25,000-99,000	<25,000
PT – increase by factor	1.0-1.10 × ULN	1.11-1.20 × ULN	1.21-1.25 × ULN	>1.25 × ULN
PTT – increase by factor	1.0-1.2 × ULN	1.21-1.4 × ULN	1.41-1.5 × ULN	>1.5 × ULN
Fibrinogen increase – mg/dL	400-500	501-600	>600	–
Fibrinogen decrease – mg/dL	150-200	125-149	100-124	<100 or associated with gross bleeding or disseminated intravascular coagulation

PPT = partial thromboplastin time; PT = prothrombin time; ULN = upper limit of normal; WBC = white blood cell.

<sup>a</sup> The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

<b>Urine<sup>a</sup></b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)</b>
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization or hyperglycemia
Blood (microscopic) – red blood cells per high power field	1-10	11-50	>50 and/or gross blood	Hospitalization or packed red blood cells transfusion

<sup>a</sup> The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

### **19.3. List of Potentially Immune-Mediated Medical Conditions**

#### **Gastrointestinal disorders**

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

#### **Liver disorders**

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

#### **Metabolic diseases**

- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

#### **Musculoskeletal disorders**

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

#### **Neuroinflammatory disorders**

- Acute disseminated encephalomyelitis, including site-specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)

- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis
- Lambert-Eaton syndrome

**Skin disorders**

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid, and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

**Vasculitides**

- Large vessel vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessel vasculitis including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis (type unspecified), Henoch-Schönlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

**Others**

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome

- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis